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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,506	02/26/2004	Darwin J. Prockop	57616-5001-03	4991

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,506	PROCKOP ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-777* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicants' response of December 4, 2006, to the non-final action dated May 31, 2006 has been entered. No claims were cancelled or newly added. Claims 55, 63 and 70 have been amended. The amendment appears to contain a typographical error in that claims 1-55 are initially indicated as cancelled. As base claim 55 is presented, the amendment should state that claims 1-54 are cancelled. Appropriate correction is required. Claims 55-77 are pending in the application and are under current examination.

Response to Priority

Applicants' claim for priority to parent application 08/412,066 (now patent 5,716,616) was denied in the previous office action dated May 31, 2006. Applicants' response notes that priority has been established only to PCT/US96/04407 filed 3/28/1996 and does not present arguments to rebut the finding for the lack of priority to the '066 application.

Response to Claim Objections

The previous office action of May 31, 2006 objected to claim 70 as being a substantial duplicate of claim 56 be found allowable. As Applicants' response has deferred the issue until claim 56 is deemed allowable, the objection is maintained.

Response to Claim Rejections - 35 USC § 112 - Lack of Enablement

Claims 55-77 stand rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for the claimed invention. The rejection set forth on pp. 2-10 of the office action dated May 31, 2006 is maintained for reasons of record.

Applicants disagree with the rejection, providing numerous case law setting forth the requirements in rejecting claims under the statute, and submit that the claimed invention is enabled by the as filed specification, because Applicants enjoy a presumption of compliance with 35 U.S.C. §112, first paragraph, that Applicant need not have actually reduced the invention to practice prior to filing, that enablement does not require a working example and experimentation is allowed so long as it is not undue. Applicants' arguments have been fully considered, but are

not found persuasive, because the nature of the invention claimed by Applicants, broadly encompassing methods of administering systemically or intraperitoneally, autologous, allogeneic or syngeneic bone marrow stromal cells wherein the cells differentiate into various cell types, thus generating, or repairing any blood vessel in a mammal, in a tissue specific manner or treating any disease that may be associated with a vascular disorder, was not considered either predictable or well-established either at the time of the instant invention or in post-filing literature. Hence, the absence of working examples or an actual reduction to practice in Applicants' disclosure are even more pertinent in the analysis of *Wands* factors in establishing an enabled disclosure for the claimed methods of the invention.

Applicants state that if the therapeutic result from administering MSCs into a mammal in need thereof embodies the state of the art, then such experimentation would appear to be routine and therefore not undue, additionally stating that a necessary element of the invention is the appreciation of the ability of MSCs to form blood vessels or otherwise cells of the blood vessels, thus the practice of the invention does not require reduction to practice of the therapeutic result. Such is not persuasive, because the method of generating a blood vessel or differentiating into any type of cell of the blood vessel, or repairing blood vessels to treat any disease associated with a defect in a blood vessel, following systemic or intraperitoneal administration of a mixed population of culture expanded bone marrow derived stromal cells is not embodied by the state of the art, as set forth in the previous office action.

Applicants assert that the examiner neglects to mention that the prior art is silent on the ability of the transplanted MSCs to migrate following transplantation to populate several connective tissues and also diffusely incorporated into the mesenchymal parenchyma of lung. In response, it is not clear what such assertion is intended to support, other than highlight that systemic administration of MSCs would result in the dilution of said cells in the animal and would further introduce stem cells to undesired locations wherein subsequent differentiation of the cells into various different lineages could complicate, rather treat a disease state. The instant specification teaches that the invention is "based upon the discovery that stromal cells introduced into patients by the bloodstream, develop into bone cartilage and lung". Additionally stating: "Similarly, it is believed that stromal cells will also develop into cells of the dermis, blood vessels, heart and kidneys, or throw off daughter cells that will do so." (page 8, line 14-29). As

indicated in the previous office action: "it would require undue experimentation to demonstrate that systemic or intraperitoneal administration of stromal cells would result in the proper differentiation and generation or repair of blood vessels at the site where said blood vessels are required, and not at undesired sites, for the methods of the instant application."

With respect to Nagaya et al., Applicants cite *In re Koller* and point out that it is impermissible to use a later factual reference to determine the application is enabled or described as required under 35 U.S.C. 112, first paragraph, and that the teaching of Nagaya is taken out of context because the major contribution of the article demonstrating improved cardiac function by MSCs, partly due to MSCs differentiating into vascular endothelial cells is overlooked. Such is not in fact the case, because the teachings of Nagaya's abstract were summarized in the first office action. Additionally, Applicants further state Nagaya's caution that "the limitation of this study is that the cell population may be mixed, rather than limited to MSCs" is not applicable to the present invention, because the pending claims are directed to bone marrow stromal cells which are defined in the specification to refer to MSCs or adherent cells.

In response, it is maintained that deficiencies in the claimed methods of the instant invention observed in post-filing art are not negatived by such observation. As stated in MPEP 2164.05(a), the specification must be enabling as of the filing date. A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling. If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993).

Further, Nagaya's observation is very much on point, because the instant specification notes that donor cells from marrow are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32). Thus, the cultured stromal cells of the instant invention as demonstrated by the instant disclosure are a mixed population of cells.

Nagaya et al. additionally noted that a low percentage of MSC migration to the heart, and further showed only a small percentage of transplanted MSCs were incorporated into the heart (first column, p. H2676). These observations are important considerations in the use of MSCs in

any treatment method, as they highlight the difficulty of delivery of MSCs to a particular target site, and the potential for detrimental neovascularization at physiological locations where such vascularization is not required. Applicants have not addressed this issue in their response.

With respect to Zisch et al., Applicants point out that endothelial progenitor cells are not the same as MSCs (to which instant claims are directed), and therefore, it is inappropriate for the examiner to rely on this reference. Such is not found persuasive, because Zisch et al. describe the application of autologous endothelial stem/progenitor cells (EPCs) derived from bone marrow, for incorporation into sites of new vessel growth for the improvement of regional blood flow (Abstract). Further, Applicants have acknowledged that MSCs differentiate into endothelial cells to contribute to blood vessel formation, thus it is incumbent on Applicants to specifically demonstrate how autologous endothelial stem/progenitor cells derived from bone marrow are different from the instantly claimed cells, and further, why the observations of Zisch et al. in regard to the plasticity of the stem cells resulting in the cells developing into a number of different cell types would not be applicable to the cells of the instant invention, wherein the systemic and intraperitoneal routes of administration of MSCs could result in transplantation at numerous sites in a mammal, causing potential undesired differentiation that would likely alter the physiological state of the mammal by providing paracrine growth factor/cytokine signals; especially in view of the instant specification's disclosure that the MSCs introduced into patients by the bloodstream develop into bone cartilage, dermis, heart, kidneys and blood vessels.

With respect to Dzau et al., Applicants assert that the reference is also directed to EPCs, and therefore defer in making arguments with respect to the reference until the examiner has established a reasonable basis to question the enablement provided by the invention, citing *In re Wright*. In response, Applicants are directed to the foregoing commentary regarding EPCs. Additionally, it is stated for the record that even if endothelial progenitor cells and MSCs were unrelated in function, Applicants have not provided any evidence that the shortcomings attributed to autologous or allogeneic transplantation of EPCs, as highlighted by Dzau et al. would not also apply MSCs. Namely, the functional impairment of the cells in patients with cardiovascular diseases, and the importance of the purity and developmental stage of the cells used for transplantation.

Finally, Applicants have failed to address the observations of Yoon et al., that injection of total bone marrow cells into the heart of infracted rats could potentially lead to severe intramyocardial calcifications, bringing into attention the potential risks of transplanting unselected bone marrow cells, further cautioning against their premature use in the clinical setting. Further, exogenous mobilization of bone marrow with hematopoietic growth factors and other endothelial growth factors may recruit progenitor cells to sites of occult neoplasia, leading to vascularization of dormant tumors. In addition, mobilization could potentially accelerate progression of atherosclerotic plaque by recruiting inflammatory and vascular smooth muscle cell progenitor cells into the plaque, contributing to neointima hyperplasia and transplant arteriopathy, as well as contribution to allograft vasculopathy by promoting neovascularization of the plaque.

Thus, contrary to Applicants' assertion that Nagaya et al. demonstrate post-filing reduction to practice, the nature of the invention is not reasonably predictable given the lack of guidance in the specification, for the generation, repair or treatment of conditions requiring neovascularization to generate a blood vessel in a mammal and treat any vascular disease, following systemic or intraperitoneal administration of unpurified culture expanded bone marrow MSCs. It would require further and undue experimentation for a person of ordinary skill in the art to demonstrate the targeted delivery of MSCs to a desired site and the generation of a blood vessel from culture expanded stromal cells and the prevention of inappropriate neovascularization or unwanted angiogenesis, to make and use the claimed invention.

Therefore the rejection of claims 55-77 is maintained for reasons of record and the discussion set forth above.

Response to Claim Rejections - 35 USC § 102 & 35 USC § 103

Claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 were rejected under 35 U.S.C. 102(a) as being anticipated by Boisvert et al., claims 55, 58, 62-63, 65, 69-70, 73, and 77 were rejected under 35 U.S.C. 102(e) as being anticipated by Caplan et al.; claims 57-58, 61, 64-65, 68, 72-73 and 76 were rejected under 35 U.S.C. §103(a) as being unpatentable over Boisvert et al., in view of Enright et al.; and claims 62, 69, and 77 were rejected under 35 U.S.C. §103(a) as being unpatentable over Boisvert et al. (of record), in view of Enright et al., and further in view of Caplan et al., in the office action dated May 31, 2006.

Upon further consideration and in view of the deficiencies in the evidence of record regarding the contribution of MSCs to blood vessel generation and disease treatment, the previous rejections are hereby withdrawn. Applicants' arguments are therefore moot in view of the withdrawl of the rejections. It is noted that should additional evidence regarding the contribution of bone marrow stromal cells to neovascularization become of record, the rejections of the claims over the cited prior art may be reapplied.

Response to Obviousness Type Double Patenting

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-70 of copending Application No. 10/423,232. The rejection set forth on p. 15 of the previous office action dated May 31, 2006 is maintained for claims 55-77 for reasons of record.

Applicants have not rebutted the rejection and have requested that the rejection be held in obeyance until allowed claims are indicated. However, in the absence of a terminal disclaimer the rejection of the claims is maintained.

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-28 of copending

Application No. 10/844,235. The rejection set forth on p. 16 of the previous office action dated May 31, 2006 is maintained for claims 55-77 for reasons of record.

Applicants have not addressed this rejection.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

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Examiner, USPTO, AU 1633

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PRIMARY EXAMINER